CLAIMS AS FILED ON JUNE 21, 2002

What is claimed is:

1. A method of treating vascular inflammatory pathologies involving TNF in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

2. A method of treating vascular inflammatory pathologies involving TNF in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, said epitope determined using the Gysen method with overlapping decapeptides of human TNF-alpha, said peptides beginning with every second amino acid and synthesized on polyethylene pins.

3. A method of treating vascular inflammatory pathologies involving TNF in a human comprising administering to the human an effective TNF-inhibiting amount of chimeric anti-TNF antibody cA2.

4. A method for treating vascular inflammatory pathologies involving TNF in a human comprising administering to the human at least one monoclonal antibody cA2, or a TNF binding fragment thereof.

5. A method of treating vascular inflammatory pathologies involving TNF in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and competitively inhibits binding of TNF to monoclonal antibody cA2.

6. A method of treating vascular inflammatory pathologies involving TNF in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, said epitope determined using the Gysen method with overlapping decapeptides of human TNF-alpha, said peptides beginning with every second amino acid and synthesized on polyethylene pins.

7. A method of treating vascular inflammatory pathologies involving TNF in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.

8. A method of treating vascular inflammatory pathologies involving TNF in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 human constant region and a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.

9. The method of Claim 7 wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

10. The method of Claim 8 wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

11. A method according to Claim 1, wherein said vascular inflammatory pathology is at least one of Kawasaki's pathology and disseminated intravascular coagulation.

12. A method according to Claim 2, wherein said vascular inflammatory pathology is at least one of Kawasaki's pathology and disseminated intravascular coagulation.

13. A method according to Claim 3, wherein said vascular inflammatory pathology is at least one of Kawasaki's pathology and disseminated intravascular coagulation.

14. A method according to Claim 4, wherein said vascular inflammatory pathology is at least one of Kawasaki's pathology and disseminated intravascular coagulation.

15. A method according to Claim 5, wherein said vascular inflammatory pathology is at least one of Kawasaki's pathology and disseminated intravascular coagulation.

16. A method according to Claim 6, wherein said vascular inflammatory pathology is at least one of Kawasaki's pathology and disseminated intravascular coagulation.

17. A method according to Claim 7, wherein said vascular inflammatory pathology is at least one of Kawasaki's pathology and disseminated intravascular coagulation.

18. A method according to Claim 8, wherein said vascular inflammatory pathology is at least one of Kawasaki's pathology and disseminated intravascular coagulation.

CLAIMS AS FILED ON JUNE 28, 2002

What is claimed is:

1. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

2. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody cA2, or a TNF binding fragment thereof.

3. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

4. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

5. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF

chimeric antibody, wherein said anti-TNF chimeric antibody does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

6. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.

7. The method of Claim 6, wherein the non-human variable region is murine.

8. The method of Claim 6, wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

9. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human a single or divided 0.1 - 100 mg/kg dose of an anti-TNF chimeric antibody, wherein said anti-TNF antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

10. The method of Claim 9, wherein the single or divided dose of anti-TNF chimeric antibody is selected from the group consisting of: a 0.1 - 1 mg/kg dose, a 1.0 - 5 mg/kg dose, a 5 - 10 mg/kg dose and a 10 - 20 mg/kg dose.

11. The method of Claim 1, wherein the anti-TNF chimeric antibody is administered to the human by means of parenteral administration.

12. The method of Claim 1, wherein the anti-TNF chimeric antibody is administered to the human by means of intravenous administration, subcutaneous administration, or intramuscular administration.

13. The method of Claim 1, wherein the anti-TNF chimeric antibody is administered orally.

14. The method of Claim 1 further comprising administering to the human an effective amount of a therapeutic agent selected from the group consisting of: disease-modifying anti-rheumatic drugs, anti-inflammatory agents, anti-neoplastic agents, radionuclides, radiotherapeutics, immunosuppressives, cytotoxic drugs, monoclonal antibodies, murine antibodies, chimeric antibodies, antibody fragments, antibody regions, lymphokines, cytokines, hemopoietic growth factors and immunoglobulins.

15. The method of Claim 14, wherein the therapeutic agent is a disease-modifying anti-rheumatic drug.

16. The method of Claim 15, wherein the disease-modifying anti-rheumatic drug is selected from the group consisting of: auranofin, azathioprine, chloroquine, D-penicillamine, gold sodium thiomalate hydroxychloroquine, Myocrisin and sulfasalzine methotrexate.

17. The method of Claim 14, wherein the therapeutic agent is an anti-inflammatory agent.

18. The method of Claim 17, wherein the anti-inflammatory agent is selected from the group consisting of: pentasa, mesalazine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac and indomethacin, aspirin and ibuprofen.

19. The method of Claim 14, wherein the therapeutic agent is an anti-neoplastic agent.

20. The method of Claim 19, wherein the anti-neoplastic agent is selected from the group consisting of: daunorubicin, doxorubicin, Mitomycin C and cyclophosphamide.

21. The method of Claim 14, wherein the therapeutic agent is a pain control agent.

22. The method of Claim 21, wherein the pain control agent is selected from the group consisting of: paracetamol and dextropropoxyphene.

23. The method of Claim 1 further comprising administering to the human an effective amount of at least one therapeutic agent selected from the group consisting of: at least one antibiotic and at least one steroid.

24. The method of Claim 1, wherein the anti-TNF chimeric antibody is of immunoglobulin class IgG1, IgG2, IgG3, IgG4, or IgM.

25. The method of Claim 1, wherein the anti-TNF chimeric antibody is a fragment selected from the group consisting of Fab, Fab', $F(ab')_2$ and Fv.

26. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1

constant region and competitively inhibits binding of TNF to monoclonal antibody cA2.

27. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

28. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

29. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

30. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

31. A method of treating a TNF-mediated heart pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5 and an IgG1 human constant region.

32. The method of Claim 31, wherein the non-human variable region is murine.

33. The method of Claim 31, wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

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AOC/DES/cmm
July 22, 2002

CLAIMS AS FILED ON JULY 18, 2002

What is claimed is:

1. A human anti-TNF antibody or antigen-binding fragment thereof that competitively inhibits binding of A2 or cA2 to human TNF-ÿ.

2. The human antibody or antigen-binding fragment of Claim 1, wherein the antibody or antigen-binding fragment comprises a human constant region and a human variable region.

3. The human antibody or antigen-binding fragment of Claim 1, which comprises at least one human light chain and at least one human heavy chain.

4. The human antibody or antigen-binding fragment of Claim 3, wherein the light chain comprises all complementarity determining regions of the light chain of A2 or cA2.

5. The human antibody or antigen-binding fragment of Claim 3, wherein the heavy chain comprises all complementarity determining regions of the heavy chain of A2 or cA2.

6. The human antibody or antigen-binding fragment of Claim 3, wherein the light chain comprises all complementarity determining regions of the light chain of A2 or cA2 and the heavy chain comprises all complementarity determining regions of the heavy chain of A2 or cA2.

7. A human anti-TNF antibody or antigen-binding fragment thereof, wherein said anti-TNF antibody or antigen-binding fragment binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

8. A human anti-TNF antibody or antigen-binding fragment thereof, wherein said anti-TNF antibody or antigen-binding fragment binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

9. A human anti-TNF antibody or antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment has epitopic specificity identical to A2 or cA2.

10. A human anti-TNF antibody or antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment comprises the complementarity determining regions of A2 or cA2.

11. A composition comprising the antibody or antigen-binding fragment of Claim 1, and a pharmaceutically acceptable carrier.

12. The human antibody or antigen-binding fragment of Claim 1, which has specificity for a neutralizing epitope of human TNF-ÿ.

13. The human antibody or antigen-binding fragment of Claim 1, which binds with high affinity to a neutralizing epitope of human TNF-ÿ *in vivo*.

14. The human antibody or antigen-binding fragment of Claim 13, wherein said binding of the antibody or antigen-binding fragment to human TNF-ÿ inhibits a pathological activity of human TNF-ÿ.

15. The human antibody or antigen-binding fragment of Claim 13, wherein said affinity is at least 10^8 liter/mole, measured as an association constant (Ka).

16. The human antibody or antigen-binding fragment of Claim 1, which is of immunoglobulin class IgG1, IgG2, IgG3, IgG4 or IgM.

17. The human antibody or antigen-binding fragment of Claim 1, wherein the anti-TNF chimeric antibody is a fragment selected from the group consisting of Fab, Fab', $F(ab')_2$ and Fv.

18. A human anti-TNF antibody or antigen-binding fragment thereof, comprising an IgG1 constant region, wherein said anti-TNF antibody or antigen-binding fragment competitively inhibits binding of A2 or cA2 to human TNF-ÿ.

19. The human antibody or antigen-binding fragment of Claim 18, wherein the antibody or antigen-binding fragment comprises a human constant region and a human variable region.

20. The human antibody or antigen-binding fragment of Claim 18, which comprises at least one human light chain and at least one human heavy chain.

21. The human antibody or antigen-binding fragment of Claim 20, wherein the light chain comprises all complementarity determining regions of the light chain of A2 or cA2.

22. The human antibody or antigen-binding fragment of Claim 20, wherein the heavy chain comprises all complementarity determining regions of the heavy chain of A2 or cA2.

23. The human antibody or antigen-binding fragment of Claim 20, wherein the light chain comprises all complementarity determining regions of the light chain of A2 or cA2 and the heavy chain comprises all complementarity determining regions of the heavy chain of A2 or cA2.

24. A human anti-TNF antibody or antigen-binding fragment thereof comprising an IgG1 constant region, wherein said anti-TNF antibody or antigen-binding fragment binds to at

least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

25. A human anti-TNF antibody or antigen-binding fragment thereof comprising an IgG1 constant region, wherein said anti-TNF antibody or antigen-binding fragment binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

26. A human antibody or antigen-binding fragment thereof, comprising an IgG1 constant region, wherein said antibody or antigen-binding fragment has epitopic specificity identical to A2 or cA2.

27. A human antibody or antigen-binding fragment thereof, comprising an IgG1 constant region, and wherein said antibody or antigen-binding fragment comprises the complementarity determining regions of A2 or cA2.

28. A composition comprising the antibody or antigen-binding fragment of Claim 18 and a pharmaceutically acceptable carrier.

29. The human antibody or antigen-binding fragment of Claim 18, wherein the antigen binding portion has specificity for a neutralizing epitope of human TNF-ÿ.

30. The human antibody or antigen-binding fragment of Claim 18, which binds with high affinity to a neutralizing epitope of human TNF-ÿ *in vivo*.

31. The human antibody or antigen-binding fragment of Claim 18, wherein said binding of the antibody or antigen-binding fragment to human TNF-ÿ inhibits a pathological activity of human TNF-ÿ.

32. The human antibody or antigen-binding fragment of Claim 31, wherein said affinity is at least 10^8 liter/mole, measured as an association constant (Ka).

33. The human antibody or antigen-binding fragment of Claim 18, which is of immunoglobulin class IgG1, IgG2, IgG3, IgG4 or IgM.

34. A human light chain that specifically binds human TNFÿ and competitively inhibits binding of A2 or cA2 to human TNF-ÿ, said human light chain consisting of the complementarity determining regions of the light chain of A2 or cA2, and a human light chain framework region.

35. A human heavy chain that specifically binds human TNFÿ and competitively inhibits binding of A2 or cA2 to human TNF-ÿ, said human heavy chain consisting of the complementarity determining regions of the heavy chain of A2 or cA2, and a human heavy chain framework region.

36. An isolated nucleic acid comprising a nucleotide sequence encoding a human light chain of Claim 34.

37. An isolated nucleic acid comprising a nucleotide sequence encoding a human heavy chain of Claim 35.

38. An expression vector comprising nucleic acid encoding a human light chain of Claim 34.

39. An expression vector comprising nucleic acid encoding a human heavy chain of Claim 35.

40. A host cell comprising the expression vector of Claim 38.

41. A host cell comprising the expression vector of Claim 39.

42. An expression vector comprising nucleic acid encoding the human antibody or antigen-binding fragment thereof of Claim 1.

43. A host cell comprising the expression vector of Claim 42.

Docket No.:0975.1005-023

CLAIMS AS FILED ON JULY 29, 2002

What is claimed is:

1. A humanized anti-TNF antibody or antigen-binding fragment thereof, comprising at least one complementarity determining region of nonhuman origin, wherein said anti-TNF antibody or antigen-binding fragment competitively inhibits binding of A2 or cA2 to human TNF-α.

2. The humanized antibody or antigen-binding fragment of Claim 1, which comprises a human constant region.

3. The humanized antibody or antigen-binding fragment of Claim 1, which comprises at least one human framework region.

4. The humanized antibody or antigen-binding fragment of Claim 1, wherein at least one complementarity determining region is of murine origin.

5. The humanized antibody or antigen-binding fragment of Claim 1, wherein all of the complementarity determining regions are of murine origin.

6. The humanized antibody or antigen-binding fragment of Claim 1, which comprises at least one light chain having at least one complementarity determining region of A2 or cA2.

Current Claims for Application 10/209,795

7. The humanized antibody or antigen-binding fragment of Claim 1, which comprises at least one heavy chain having at least one complementarity determining region of A2 or cA2.

8. The humanized antibody or antigen-binding fragment of Claim 1, which comprises at least one light chain and at least one heavy chain, wherein said light chain and heavy chain each have all complementarity determining regions of A2 or cA2.

9. A humanized antibody or antigen-binding fragment thereof, comprising a constant region of human origin and a variable region, wherein said variable region comprises:

(a) at least one complementarity determining region derived from an antibody of murine origin that binds to human TNF-α; and

(b) at least one framework region of human origin,

and wherein said antibody or antigen-binding fragment competitively inhibits binding of A2 or cA2 to human TNF-α.

10. A humanized antibody or antigen-binding fragment thereof, comprising:

(a) at least one light chain comprising at least one complementarity determining region of an antibody of nonhuman origin which binds human TNF-α and at least one framework region of at least one light chain of human origin; and

(b) at least one heavy chain comprising at least one complementarity determining region of an antibody of nonhuman origin which binds

human TNF-α and at least one framework region of a heavy chain of human origin,

wherein the antibody or antigen-binding fragment competitively inhibits binding of A2 or cA2 to human TNF-α.

11. The humanized antibody or antigen-binding fragment of Claim 10, wherein at least one light chain comprises at least one complementarity determining region of at least one light chain of A2 or cA2.

12. The humanized antibody or antigen-binding fragment of Claim 10, wherein at least one heavy chain comprises at least one complementarity determining region of at least one heavy chain of A2 or cA2.

13. The humanized antibody or antigen-binding fragment of Claim 10, wherein at least one light chain comprises all complementarity determining regions of at least one light chain of A2 or cA2.

14. The humanized antibody or antigen-binding fragment of Claim 10, wherein at least one heavy chain comprises all complementarity determining regions of at least one heavy chain of A2 or cA2.

15. The humanized antibody or antigen-binding fragment of Claim 10, wherein at least one light chain comprises all complementarity determining regions of at least one light chain of A2 or cA2 and the heavy chain comprises all complementarity determining regions of at least one heavy chain of A2 or cA2.

16. A humanized anti-TNF antibody or antigen-binding fragment thereof, wherein said anti-TNF antibody or antigen-binding fragment comprises at least one complementarity determining region of nonhuman origin and at least one framework region having at least one human residue, and wherein said anti-TNF antibody or antigen-binding fragment binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

17. A humanized anti-TNF antibody or antigen-binding fragment thereof, comprising at least one complementarity determining region of nonhuman origin and at least one framework region having at least one human residue, and wherein said anti-TNF antibody or antigen-binding fragment binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

18. A humanized antibody or antigen-binding fragment thereof, comprising at least one complementarity determining region of nonhuman origin and at least one framework region having at least one human residue, wherein said antibody or antigen-binding fragment has epitopic specificity identical to A2 or cA2.

19. A humanized antibody or antigen-binding fragment thereof, comprising at least one framework region having at least one human residue, wherein said antibody or antigen-binding fragment comprises the complementarity determining regions of A2 or cA2.

20. An antibody or antigen-binding fragment thereof which specifically binds to human TNF-α, said antibody or antigen-binding fragment comprising at least one light chain comprising at least one light chain complementarity determining region of A2 or cA2 and at least one light chain variable region framework sequence from a human light chain.

21. An antibody or antigen-binding fragment thereof which specifically binds to human TNF-α, said antibody or antigen-binding fragment comprising at least one heavy chain comprising at least one heavy chain complementarity determining region of A2 or cA2 and at least one heavy chain variable region framework sequence from a human heavy chain.

22. A composition comprising the antibody or antigen-binding fragment of Claim 1, and a pharmaceutically acceptable carrier.

23. The humanized antibody or antigen-binding fragment of Claim 1, which has specificity for a neutralizing epitope of human TNF-α.

24. The humanized antibody or antigen-binding fragment of Claim 1, which binds with high affinity to a neutralizing epitope of human TNF-α *in vivo*.

25. The humanized antibody or antigen-binding fragment of Claim 24, wherein said binding of the antibody or antigen-binding fragment to human TNF-α inhibits a pathological activity of human TNF-α.

26. The humanized antibody or antigen-binding fragment of Claim 24, wherein said affinity is at least 10^8 liter/mole, measured as an association constant (Ka).

27. The humanized antibody or antigen-binding fragment of Claim 1, which is of immunoglobulin class IgG1, IgG2, IgG3, IgG4 or IgM.

28. The humanized antibody or antigen-binding fragment of Claim 1, which is selected from the group consisting of Fab, Fab', $F(ab')_2$ and Fv.

29. An anti-TNF antibody or antigen-binding fragment thereof, comprising at least one antigen binding residue of nonhuman origin and at least one framework region of human origin, wherein said anti-TNF antibody or antigen-binding fragment competitively inhibits binding of A2 or cA2 to human TNF-α.

30. An antibody or antigen-binding fragment thereof, comprising a constant region of human origin and a variable region, wherein said variable region comprises:

(a) at least one antigen binding residue derived from an antibody of murine origin that binds to human TNF-α; and

(b) at least one framework region of human origin,

and wherein said antibody or antigen-binding fragment competitively inhibits binding of A2 or cA2 to human TNF-α.

31. An antibody or antigen-binding fragment thereof, comprising:

(a) at least one light chain comprising at least one antigen binding residue of an antibody of nonhuman origin which binds human TNF-α, and at least one framework region of at least one light chain of human origin; and

(b) at least one heavy chain comprising at least one antigen binding residue of an antibody of nonhuman origin which binds human TNF-α, and at least one framework region of at least one heavy chain of human origin,

wherein the antibody or antigen-binding fragment competitively inhibits binding of A2 or cA2 to human TNF-α.

32. An anti-TNF antibody or antigen-binding fragment thereof, wherein said anti-TNF antibody or antigen-binding fragment comprises at least one antigen binding residue of nonhuman origin and at least one framework region having at least one human residue, and wherein said anti-TNF antibody or antigen-binding fragment binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

33. An anti-TNF antibody or antigen-binding fragment thereof, comprising at least one antigen binding residue of nonhuman origin and at least one framework region having at least one human residue, and wherein said anti-TNF antibody or antigen-binding fragment binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

34. An antibody or antigen-binding fragment thereof, comprising at least one antigen binding residue of nonhuman origin and at least one framework region having at least one human residue, and wherein said antibody or antigen-binding fragment has epitopic specificity identical to A2 or cA2.

35. An antibody or antigen-binding fragment thereof, comprising at least one framework region having at least one human residue, wherein said antibody or antigen-binding fragment comprises the antigen binding residues of A2 or cA2.

36. An antibody or antigen-binding fragment thereof which specifically binds to human TNF-α, said antibody or antigen-binding fragment comprising at least one light chain comprising at least one light chain antigen binding residue of A2 or cA2 and at least one light chain variable region framework sequence from a human light chain.

37. An antibody or antigen-binding fragment thereof which specifically binds to human TNF-α, said antibody or antigen-binding fragment comprising at least one heavy chain comprising at least one heavy chain antigen binding residue of A2 or cA2 and at least one heavy chain variable region framework sequence from a human heavy chain.

38. A composition comprising the antibody or antigen-binding fragment of Claim 29, and a pharmaceutically acceptable carrier.

39. A humanized anti-TNF antibody or antigen-binding fragment thereof, comprising an IgG1 constant region and at least one complementarity determining region of

nonhuman origin, wherein said anti-TNF antibody or antigen-binding fragment competitively inhibits binding of A2 or cA2 to human TNF-α.

40. A humanized antibody or antigen-binding fragment thereof, comprising an IgG1 constant region of human origin and a variable region, wherein said variable region comprises:

(a) at least one complementarity determining region derived from an antibody of murine origin that binds to human TNF-α; and

(b) at least one framework region of human origin,

and wherein said antibody or antigen-binding fragment competitively inhibits binding of A2 or cA2 to human TNF-α.

41. A humanized antibody or antigen-binding fragment thereof, comprising:

(a) at least one light chain comprising at least one complementarity determining region of an antibody of nonhuman origin which binds human TNF-α and at least one framework region of at least one light chain of human origin;

(b) at least one heavy chain comprising at least one complementarity determining region of an antibody of nonhuman origin which binds human TNF-α, and at least one framework region of a heavy chain of human origin; and

(c) an IgG1 constant region,

wherein the antibody or antigen-binding fragment competitively inhibits binding of A2 or cA2 to human TNF-α.

42. A humanized anti-TNF antibody or antigen-binding fragment thereof, comprising at least one complementarity determining region of nonhuman origin, at least one framework region having at least one human residue and an IgG1 constant region, wherein said anti-TNF antibody or antigen-binding fragment binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

43. A humanized anti-TNF antibody or antigen-binding fragment thereof, comprising at least one complementarity determining region of nonhuman origin, at least one framework region having at least one human residue and an IgG1 constant region, wherein said anti-TNF antibody or antigen-binding fragment binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

44. A humanized antibody or antigen-binding fragment thereof, comprising at least one complementarity determining region of nonhuman origin, at least one framework region having at least one human residue and an IgG1 constant region, wherein said antibody or antigen-binding fragment has epitopic specificity identical to A2 or cA2.

45. A humanized antibody or antigen-binding fragment thereof, comprising at least one framework region having at least one human residue and an IgG1 constant region, wherein said antibody or antigen-binding fragment comprises the complementarity determining regions of A2 or cA2.

46. A humanized anti-TNF antibody or antigen-binding fragment thereof that specifically binds to human TNF-α and competitively inhibits binding of A2 or cA2 to human TNF.

47. A humanized anti-TNF antibody or antigen-binding fragment thereof that specifically binds to human TNF-α and has epitopic specificity identical to A2 or cA2.

48. A humanized antibody or antigen-binding fragment thereof which specifically binds to human TNF-α, comprising the complementarity determining regions of A2 or cA2.

49. A light chain that specifically binds human TNF-α, said light chain comprising the complementarity determining regions of at least one light chain of A2 or cA2 and at least one human light chain framework region.

50. A heavy chain that specifically binds human TNF-α, said heavy chain comprising the complementarity determining regions of at least one heavy chain of A2 or cA2 and at least one human heavy chain framework region.

51. A light chain that specifically binds human TNF-α, said light chain comprising the antigen binding residues of at least one light chain of A2 or cA2 and at least one human light chain framework region.

52. A heavy chain that specifically binds human TNF-α, said heavy chain comprising the antigen binding residues of at least one heavy chain of A2 or cA2 and at least one human heavy chain framework region.

53. An isolated nucleic acid comprising a sequence encoding a light chain of Claim 49.

54. An isolated nucleic acid comprising a sequence encoding a heavy chain of Claim 50.

55. An expression vector comprising a gene encoding a humanized immunoglobulin light chain, said gene comprising a nucleotide sequence encoding at least one complementarity determining region derived from at least one light chain of A2 and at least one framework region derived from at least one light chain of human origin.

56. A host cell comprising the expression vector of Claim 55.

57. An expression vector comprising a gene encoding a humanized immunoglobulin heavy chain, said gene comprising a nucleotide sequence encoding at least one complementarity determining region derived from at least one heavy chain of A2 and at least one framework region derived from at least one heavy chain of human origin.

58. A host cell comprising the expression vector of Claim 57.

59. A host cell comprising a first recombinant nucleic acid encoding a humanized immunoglobulin light chain and a second recombinant nucleic acid encoding a humanized immunoglobulin heavy chain, said first nucleic acid comprising a nucleotide sequence encoding at least one complementarity determining region derived from at least one light chain of A2 or cA2 and at least one framework region derived from at least one light chain of human origin; and said second nucleic acid comprising a nucleotide sequence encoding at least one complementarity determining region derived from at least one heavy chain of A2 or cA2 and at least one framework region derived from at least one heavy chain of human origin.

60. A method of preparing a humanized antibody or antigen-binding fragment thereof comprising maintaining a host cell of Claim 56 under conditions appropriate for expression of a humanized antibody or antigen-binding fragment thereof, wherein humanized immunoglobulin chains are expressed and a humanized antibody or antigen-binding fragment is produced.

61. A method of making a humanized antibody or antigen-binding fragment thereof that selectively binds human TNF-α, said antibody or antigen-binding fragment thereof comprising an antigen binding region of nonhuman origin and at least a portion of an antibody of human origin, said method comprising:

(a) determining at least one complementarity determining region of an antibody of nonhuman origin that specifically binds human TNF-α and competitively inhibits A2 or cA2;

(b) obtaining a human antibody having at least one framework region amino acid sequence suitable for grafting of at least one complementarity determining region determined in (a); and

(c) grafting at least one complementarity determining region of (a) into at least one framework region of the human antibody of (b);

wherein a humanized antibody or antigen-binding fragment thereof that selectively binds to human TNF-α is made.

62. The method of Claim 61, wherein the antibody of nonhuman origin is of murine origin.

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CLAIMS AS FILED ON JULY 29, 2002

What is claimed is:

1. A method of treating a TNF-mediated lung pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

2. A method of treating a TNF-mediated lung pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody cA2, or a TNF binding fragment thereof.

3. A method of treating a TNF-mediated lung pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

4. A method of treating a TNF-mediated lung pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

5. A method of treating a TNF-mediated lung pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises a non-human variable

region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.

6. The method of Claim 5, wherein the non-human variable region is murine.

7. The method of Claim 5, wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

8. A method of treating a TNF-mediated lung pathology in a human comprising administering to the human a single or divided 0.1 - 100 mg/kg dose of an anti-TNF chimeric antibody, wherein said anti-TNF antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

9. The method of Claim 8, wherein the single or divided dose of anti-TNF chimeric antibody is selected from the group consisting of: a 0.1 - 1 mg/kg dose, a 1.0 - 5 mg/kg dose, a 5 - 10 mg/kg dose and a 10 - 20 mg/kg dose.

10. The method of Claim 1, wherein the anti-TNF chimeric antibody is administered to the human by means of parenteral administration.

11. The method of Claim 1, wherein the anti-TNF chimeric antibody is administered to the human by means of intravenous administration, subcutaneous administration, or intramuscular administration.

12. The method of Claim 1, wherein the anti-TNF chimeric antibody is administered orally.

13. The method of Claim 1 further comprising administering to the human an effective amount of a therapeutic agent selected from the group consisting of: disease-modifying anti-rheumatic drugs, anti-inflammatory agents, anti-neoplastic agents, radionuclides,

radiotherapeutics, immunosuppressives, cytotoxic drugs, monoclonal antibodies, murine antibodies, chimeric antibodies, antibody fragments, antibody regions, lymphokines, cytokines, hemopoietic growth factors and immunoglobulins.

14. The method of Claim 13, wherein the therapeutic agent is a disease-modifying anti-rheumatic drug.

15. The method of Claim 14, wherein the disease-modifying anti-rheumatic drug is selected from the group consisting of: auranofin, azathioprine, chloroquine, D-penicillamine, gold sodium thiomalate hydroxychloroquine, Myocrisin and sulfasalzine methotrexate.

16. The method of Claim 13, wherein the therapeutic agent is an anti-inflammatory agent.

17. The method of Claim 16, wherein the anti-inflammatory agent is selected from the group consisting of: pentasa, mesalazine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac and indomethacin, aspirin and ibuprofen.

18. The method of Claim 13, wherein the therapeutic agent is an anti-neoplastic agent.

19. The method of Claim 18, wherein the anti-neoplastic agent is selected from the group consisting of: daunorubicin, doxorubicin, Mitomycin C and cyclophosphamide.

20. The method of Claim 13, wherein the therapeutic agent is a pain control agent.

21. The method of Claim 20, wherein the pain control agent is selected from the group consisting of: paracetamol and dextropropoxyphene.

22. The method of Claim 1 further comprising administering to the human an effective amount of at least one therapeutic agent selected from the group consisting of: at least one antibiotic and at least one steroid.

23. The method of Claim 1, wherein the anti-TNF chimeric antibody is of immunoglobulin class IgG1, IgG2, IgG3, IgG4, or IgM.

24. The method of Claim 1, wherein the anti-TNF chimeric antibody is a fragment selected from the group consisting of Fab, Fab', $F(ab')_2$ and Fv.

25. A method of treating a TNF-mediated lung pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and competitively inhibits binding of TNF to monoclonal antibody cA2.

26. A method of treating a TNF-mediated lung pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

27. A method of treating a TNF-mediated lung pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

28. A method of treating a TNF-mediated lung pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5 and an IgG1 human constant region.

29. The method of Claim 28, wherein the non-human variable region is murine.

30. The method of Claim 28, wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

31. The method of Claim 1 wherein the TNF-mediated lung pathology is a chronic inflammatory disease.

32. The method of Claim 1 wherein the TNF-mediated lung pathology is associated with a heart pathology.

33. The method of Claim 1 wherein the TNF-mediated lung pathology is associated with a vascular inflammatory pathology.

CLAIMS AS FILED ON JUNE 28, 2002

What is claimed is:

1. A method of treating rheumatoid arthritis or Crohn's disease in a human comprising administering to the human a single or divided 0.5 - 15 mg/kg dose at least once every one to six weeks of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

2. A method of treating rheumatoid arthritis or Crohn's disease in a human comprising administering to the human a single or divided 0.5 - 15 mg/kg dose at least once every six weeks of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

3. The method of Claim 2, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every six weeks after the second dose.

4. The method of Claim 2, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every five weeks after the second dose.

5. The method of Claim 2, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every four weeks after the second dose.

6. The method of Claim 2, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every three weeks after the second dose.

7. The method of Claim 2, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every two weeks after the second dose.

8. The method of Claim 2, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every week after the second dose.

9. A method of treating rheumatoid arthritis or Crohn's disease in a human comprising administering to the human a single or divided 1 - 15 mg/kg dose at least every one to six weeks of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

10. The method of Claim 9, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every six weeks after the second dose.

11. The method of Claim 9, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every five weeks after the second dose.

12. The method of Claim 9, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every four weeks after the second dose.

13. The method of Claim 9, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every three weeks after the second dose.

14. The method of Claim 9, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every two weeks after the second dose.

15. The method of Claim 9, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every week after the second dose.

16. A method of treating rheumatoid arthritis or Crohn's disease in a human comprising administering to the human a single or divided 2 - 10 mg/kg dose at least once every six weeks of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

17. The method of Claim 16, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every two to six weeks after the second dose.

18. The method of Claim 16, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every four to six weeks after the second dose.

19. A method of treating rheumatoid arthritis or Crohn's disease in a human comprising administering to the human a single or divided 3-5 mg/kg dose at least once every six weeks of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

20. The method of Claim 19, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every two to six weeks after the second dose.

21. The method of Claim 19, wherein a first dose of the anti-TNF chimeric antibody is administered to the human, a second dose is administered one to four weeks after the first dose, and subsequent doses are administered every four to six weeks after the second dose.

22. The method of Claim 1, wherein the anti-TNF chimeric antibody is cA2, or a TNF binding fragment thereof.

23. The method of Claim 1, wherein said anti-TNF chimeric antibody binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

24. The method of Claim 1, wherein said anti-TNF chimeric antibody binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

25. The method of Claim 1, wherein said anti-TNF chimeric antibody does not bind to one or more epitopes included in amino acids Gysen 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

26. The method of Claim 1, wherein said anti-TNF chimeric antibody does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

27. The method of Claim 1, wherein said anti-TNF chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.

28. The method of Claim 27, wherein the non-human variable region is murine.

29. The method of Claim 27, wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

30. The method of Claim 1, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and competitively inhibits binding of TNF to monoclonal antibody cA2.

31. The method of Claim 1, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

32. The method of Claim 1, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

33. The method of Claim 1, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

34. The method of Claim 1, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

35. The method of Claim 1, wherein said anti-TNF chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5 and an IgG1 human constant region.

36. The method of Claim 35, wherein the non-human variable region is murine.

37. The method of Claim 35, wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

38. The method of Claim 1, wherein the anti-TNF chimeric antibody is administered to the human by means of parenteral administration.

39. The method of Claim 1, wherein the anti-TNF chimeric antibody is administered to the human by means of intravenous administration, subcutaneous administration, or intramuscular administration.

40. The method of Claim 1, wherein the anti-TNF chimeric antibody is administered orally.

41. The method of Claim 1 further comprising administering to the human an effective amount of a therapeutic agent selected from the group consisting of: disease-modifying anti-rheumatic drugs, anti-inflammatory agents, anti-neoplastic agents, radionuclides, radiotherapeutics, immunosuppressives, cytotoxic drugs, monoclonal antibodies, murine antibodies, chimeric antibodies, antibody fragments, antibody regions, cytokines, lymphokines, hemopoietic growth factors and immunoglobulins.

42. The method of Claim 41, wherein the therapeutic agent is a disease-modifying anti-rheumatic drug.

43. The method of Claim 42, wherein the disease-modifying anti-rheumatic drug is selected from the group consisting of: auranofin, azathioprine, chloroquine, D-penicillamine, gold sodium thiomalate hydroxychloroquine, Myocrisin and sulfasalzine methotrexate.

44. The method of Claim 41, wherein the therapeutic agent is an anti-inflammatory agent.

45. The method of Claim 44, wherein the anti-inflammatory agent is selected from the group consisting of: pentasa, mesalazine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac and indomethacin, aspirin and ibuprofen.

46. The method of Claim 41, wherein the therapeutic agent is an anti-neoplastic agent.

47. The method of Claim 46, wherein the anti-neoplastic agent is selected from the group consisting of: daunorubicin, doxorubicin, Mitomycin C and cyclophosphamide.

48. The method of Claim 41, wherein the therapeutic agent is a pain control agent.

49. The method of Claim 48, wherein the pain control agent is selected from the group consisting of: paracetamol and dextropropoxyphene.

50. The method of Claim 41, wherein the therapeutic agent is a radionuclide agent selected from the group consisting of: ^{212}Bi, ^{131}I, ^{186}Re and ^{90}Y.

51. The method of Claim 1 further comprising administering to the human an effective amount of a therapeutic agent selected from the group consisting of: antibiotics and steroids.

52. The method of Claim 1, wherein the anti-TNF chimeric antibody is of immunoglobulin class IgG1, IgG2, IgG3, IgG4 or IgM.

53. The method of Claim 1, wherein the anti-TNF chimeric antibody is a fragment selected from the group consisting of Fab, Fab', $F(ab')_2$ and Fv.